British Medical Journal.

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PULMONARY ASBESTOSIS.*

BY

W. E. COOKE, M.D., M.R.C.P.,
Director of the Pathological Department, Wigan Infirmary.

(With Special Plate.)

IN the BRITISH MEDICAL JOURNAL of July 26th, 1924 (p. 147), I published a short note on the woman who is the subject of this paper. The only similar case on record was that of a man admitted to the Charing Cross Hospital in 1899, where he died in 1900. Dr. E. L. Middleton of the Home Office kindly lent the notes of the case, and of the evidence given before the Departmental Committee on Industrial Diseases in 1906 by the late Dr. H. Montague Murray, under whose care the man had been. This patient, a man aged 33 years, had worked in the carding room of an asbestos factory for ten years prior to his admission to hospital. He informed Dr. Murray that he was the sole survivor of ten men who started work with him in the carding room; the others had died, presumably as the result of their occupation. A *post-mortem* examination was held and the diagnosis of pulmonary fibrosis was confirmed. Dr. Murray in his evidence refers to photomicrographs of lung sections which show "spicules of asbestos." These are the salient facts of the first and, down to 1924, the only record of a death due to asbestos.

That these two cases stand alone is very surprising. The asbestos industry is more than 2,000 years old, and we know that asbestos factories, up to quite recent years, have been devoid of any appliances for the prevention and extraction of dust. The remark of Dr. Murray's patient is suggestive, and medical men have long suspected asbestos dust to be the cause of lung conditions in workers in badly ventilated factories.

Asbestos is a physical paradox—a mineralogical vegetable, both fibrous and crystalline, elastic, and brittle; as capable of being carded, spun, and woven as wool, flax, or silk. A single strand can be spun to weigh less than an ounce to 100 yards, and a cloth manufactured which weighs less than 8 ounces to the square yard. It occurs in every country, but is never found in any two countries alike, nor, indeed, in any two parts of the same country.

Historical.

Asbestos is apparently indestructible, and its fire-resisting qualities were known to the ancients. The Romans mined it from the Italian Alps and the Ural Mountains. Herodotus (*circa* 450 B.C.) described a cremation cloth made from asbestos. Pliny (*circa* A.D. 50) mentions the difficulty in weaving it. Strabo (*circa* 30 B.C.) and Plutarch (*circa* A.D. 70) both speak of the wicks of the lamps of the Vestal Virgins being made from asbesta, so called because they maintained a perpetual flame without being consumed. Pausanius (*circa* A.D. 175) refers to a gold lamp made by Callimachus of Athens for Minerva, the wick of which was made of Carpasian linen, "the only linen which is not consumed by fire." Later (A.D. 1250) Marco Polo writes that he had seen Tartars using cloth that withstood fire which was made of a "Certaine Minerall of Earth found in a Mountayne."

Although its valuable properties have been known for thousands of years the modern adaptation of asbestos to the industrial arts dates from only a few years ago.

Composition.

Asbestos is one of the silicates, and its varieties are numerous. Wherever it occurs it is found associated with other minerals, more especially with chromo iron magnetite. The composition of the well known Italian Canadian fibres is as follows:

	Italian Fibre.	Canadian Chrysotile.
Silica	40.30	40.87
Magnesia	43.37	41.50
Ferrous oxide	0.87	2.81
Alumina	2.27	0.90
Water	13.72	13.55

The purest asbestos, having fibres of extraordinary length, occurs in Northern Italy. Asbestos may contain from 0.5 to 15 per cent. of iron oxide, but asbestos yarn is prepared from mineral as free as possible from iron. To get rid of the difficultly soluble iron, asbestos is soaked in orthophosphoric acid solution and washed in water before manufacture. The percentage of iron, then, is of reduced importance.

Manufacturing Process.

The process of manufacture resembles that of cotton. The crude mineral is subject to mechanical treatment in a grinding machine. The heavier rock is separated by gravity, and the remaining asbestos passed through carding, roving, and spinning machines, and from these to the weaving sheds.

During the carding process, and to a less extent in the subsequent processes, a very considerable amount of dust is generated. In up-to-date factories all machines are fitted with extractor covers and the dust removed. In the first factory where the patient the subject of this paper was employed no method of dust removal was used, and the atmospheric conditions were occasionally so bad that workers in her particular room could not see each other.

DESCRIPTION OF PLATES.

FIG. 1.—*Asbestos* fibre, the bulk of which is translucent and in which are black angular (iron-containing) fragments. These constitute a large proportion of the dust generated in manufacture. (× 150.)

FIG. 2.—Large particles of asbestos in fibrotic area of lung. (× 150.)

FIG. 3.—Particle of asbestos 350 microns in length in necrotic area of lung. (× 153.)

FIGS. 4, 3, AND 12.—Curious bodies. (× 400.)

FIGS. 5, 6, 10, AND 11.—Curious bodies showing discoid arrangement and globular ends. Fig. 6 shows particles of these bodies and granular dust in a phagocytic cell. (× 1000.)

FIG. 7.—Fibrosed lung with clusters of the curious bodies lying free in alveoli.

FIG. 8.—Fibro-caseous area with giant cells.

Figs. 1 to 6 are reproduced by kind permission of the Editor of the *Journal of the Royal Microscopical Society.*

Asbestos Fibre and Dust.

Microscopically asbestos fibre is seen to consist of two very different elements. The bulk of the fibre is translucent and glistening, with here and there black opaque angular particles (Fig. 1). Minute black granules also are present. These black particles are actually part of the fibre, but their appearance suggests a different chemical composition and different physical characters from the translucent portion. The dust generated during manufacture is seen to consist of these sharp angular particles and minute granules, suggesting, of course, that they are more brittle than the translucent part of the fibre. These particles are found in very small numbers in the finished article. Mr. T. H. Byrom, F.I.C., analysed several samples of dust, and found that the dusts containing the greater numbers of these black particles contained the largest amount of iron. The iron content of the finished article, raw material, and dust is as follows:

Finished article: Iron (as ferrous oxide)	0.1%
Crude raw material: Iron (as ferrous oxide)... ...	2.5%
Dust from carding room: Iron (as ferrous oxide) ...	18.4%

From these results it appears conclusive that the blue-stained brittle parts of the asbestos fibre are the iron-containing portions—the bugbear of the manufacturer, the cause of "dust," and a danger to the health of workers in the process of manufacture.

Clinical History of the Case.

The deceased, a woman aged 33 years, commenced work at the age of 13 years in an asbestos factory in which no provision was made for the extraction of dust. From an early age, soon after commencing work, she suffered from a cough, which did not interfere with her general health until 1917. She was then 30 years of age, and had been working thirteen years. From this time until 5 years later (1922) her attendances at work were intermittent owing to ill health. She missed occasional days, one or two periods of some weeks, until she finally ceased work in July, 1922.

Up to this she complained of cough, dyspnœa, expectoration

*"This and the two following papers on this subject were read in the Section of Preventive Medicine at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

(*Illustrating the papers by* DRS. W. E. COOKE *and* STUART MCDONALD.)



FIG. 1.



FIG. 2.

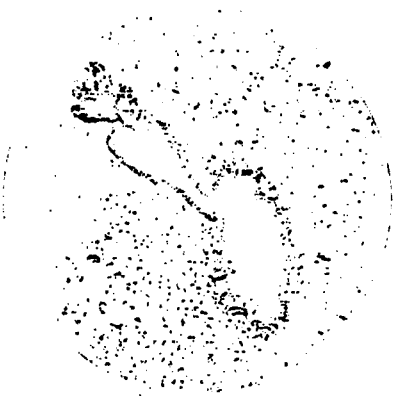


FIG. 3.



FIG. 4.



FIG. 5.

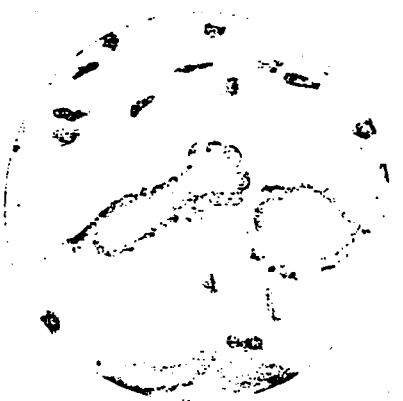


FIG. 6.

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(*Illustrating the papers by* DRS. W. E. COOKE *and* STUART MCDONALD.)

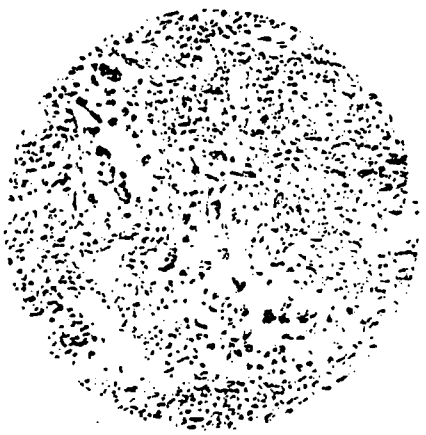


FIG. 7.



FIG. 8.



FIG. 9.



FIG. 10.



FIG. 11.

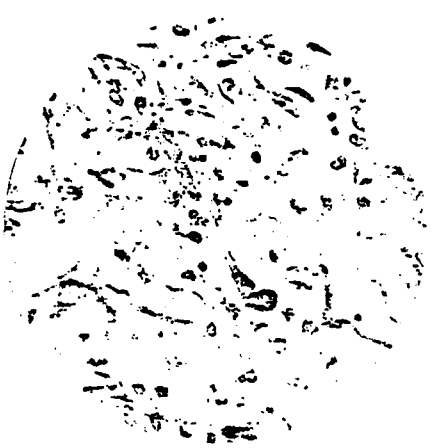


FIG. 12.

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and lassitude. The physical signs in her chest were those of fibrosis of the right lung. In July, 1922, signs of cavitation were noticed, the sputum became more profuse, with sweats and irregular temperature, and she died on March 14th, 1924.

An *x*-ray plate showed extensive fibrosis, more marked in the right lung, two calcareous glands at the root of the left lung, and two small calcareous particles in the base of the left lower lobe.

Macroscopical Appearances.

Right Lung.—The pleura is thickened over the entire surface of the lung, and shows the remains of dense adhesions to the chest wall and pericardium. The lung is firm and small. The glands at the root of the lung are large, and on section are black, show a thickened capsule, and some calcareous particles. On section, the lung is seen to be fibrosed and to a large extent airless, the lung tissue being replaced by fibrous tissue. Dense strands of fibrous tissue from the pleura intersect the lung. In the apex there is a large cavity, the size of a peeled tangerine orange. The middle and lower lobes show numerous small areas—varying in size from a hazel-nut to a pin's head—of caseation, some of which have proceeded to cavitation. The bronchi are dilated.

Left Lung.—The pleura is thickened and shows the remains of adhesions to the chest wall. The thickening and adhesions are not so marked as in the right lung. The lung is firmer than normal. At the root of the lung are two large calcareous masses, one the size of a large hazel-nut, the other about half that size—calcified tuberculous glands. The other glands are black and show peribronchitis. In the left apex there is an area of old scar tissue about the size of a sixpenny piece, and a cavity the size of a walnut. Scattered throughout the lung are small areas of denser consistence than the rest of the lung, some of which show definite calcareous particles, others small areas of caseation. There is a considerable increase in the fibrous tissue.

Three outstanding features are presented by sections from this case. The first is the enormous amount of fine granular pigment in the peribronchial fibrous tissue, walls of alveoli, and in phagocytes scattered through the sections. The particles of this dust are similar in size and shape to the black granules seen in the asbestos fibre.

The second unusual feature is the presence of large solid angular particles (Fig. 2). These are situated in areas of fibrosis and in caseating areas. They vary in size from 3 to 360 microns in length. The particles are so large—masses of them are seen in certain areas—that they must have occluded small bronchi. Fibrosis of the alveoli supplied has taken place and later necrosis, as seen in Fig. 3.

We have never seen anything parallel to this in pneumonoconiosis due to other dusts, nor have we been able to find such occurrence in literature. On comparing these large particles with asbestos dust there is a striking resemblance in sizes, shapes, and colour. In fact, it is very easy to take each single particle found in the lung sections and immediately find its brother in a slide made from the dust.

We cannot think there is any reasonable doubt that the particles in the lungs are the heavy, brittle, iron-containing fragments of asbestos fibre. The more extensive involvement of the right lung is thus explained. The heavy particles would pass more easily down the more vertical right bronchus than the horizontal left bronchus.

HISTOLOGY OF PULMONARY ASBESTOSIS.

BY

STUART McDONALD, M.D., F.R.C.P.,
Professor of Pathology, University of Durham.

(*With Special Plate.*)

My remarks are confined to the histological appearances in the lungs in this condition, with special reference to certain foreign bodies of most unusual appearance which are present both in the alveoli and interstitial substance of the lungs. The observations are based almost entirely on material supplied from the case described by Dr. Cooke. The investigation has been conducted in the pathological department of the University of Durham College of Medicine.

I may state, however, that the appearances are practically identical with those observed in a second case of this condition, sections of which I have had an opportunity of examining through the courtesy of Dr. I. M. D. Grieve of Armley, Leeds.

Histology.

Numerous sections have been made from both lungs. The changes are more marked on the right side, but the appearances in the two lungs only differ in degree. They may be summarized as follows:

1. There is well marked diffuse interstitial pneumonia with chronic bronchitis and some emphysema.
2. There is well marked anthracosis.
3. There is an extensive tuberculous condition with chronic phthisis.
4. In the alveoli, bronchi, and bronchioles, and also in the interstitial fibrotic areas, are certain foreign bodies which will be described in detail later (Fig. 7).

As this communication deals specially with the nature of the foreign bodies, the general histological features will be dealt with very briefly.

The interstitial fibrosis is such as might be expected as a result of a combination of a pneumonoconiotic condition and a chronic tuberculous infection. The typical whorled formations seen in a more purely silicotic condition are not present. There is a marked endarteritis in the smaller branches of the pulmonary arteries; some are thrombosed and organized. Many of the smaller bronchi are obliterated; some have still caseous-looking centres. Some of the alveoli show the usual metaplasia of their lining cells into cuboidal form. The fibrosed and thickened walls of the bronchi in many places gradually merge into the areas of diffuse fibrous overgrowth. There are numerous foci of lymphocytic cells among the fibroblasts. Some of these seem obviously derived from lymphoid tissue in the bronchial walls. The interstitial fibrosis is progressive. The tuberculous condition is obvious histologically. Tubercle bacilli were not detected, but the histology is characteristic. The lesions are chronic in character, and there is no special indication of an acute exacerbation. There is well marked caseous bronchitis with lymphatic spread and numerous fibro-caseous deposits with giant cell systems (see Fig. 8). The bronchi, which are not specially the seat of tuberculous change, show catarrh with peribronchial thickening. There are numerous emphysematous areas. The alveoli show, in the majority of cases, some thickening of their walls, and contain many catarrhal cells, apparently derived from the lining cells; a similar catarrhal change is seen in the terminal bronchioles, some of which are dilated.

The Foreign Bodies.

The larger black and irregularly fragmented bodies which have been described by Dr. Cooke were not very obvious in the material I examined, but were clearly seen in some microscopical preparations of his which I had the opportunity of examining. I shall not refer to them specially, but confine my attention to certain highly characteristic and much smaller bodies which are abundant in all the sections examined. Some of these are free, but many are phagocytosed by the large mononuclear cells in the alveoli (Fig. 9). Some are easily included in comparatively small phagocytic cells, but the majority are larger, varying in size from 20 μ to 70 μ, or even more in the case of certain elongated forms. The smaller bodies are rounded and homogeneous, and all have a distinct yellowish-brown colour suggesting blood pigment. The longer forms have a highly characteristic appearance, strongly suggestive of some organic structure. Most have an annular appearance, which on closer examination can be resolved into a closely set series of rounded discoid bodies (Figs. 4, 5, 10, and 11). In some cases the globular forms are arranged along the more filamentous forms and occasionally are clustered at the ends of the rods, simulating sporangia of a hyphomycetes (Figs. 5, 6, 10, and 11). Some have club-like extremities at one or both ends of the filaments. Others, again, suggest the appearance of minute crustacean forms (Fig. 10), but closer examination does not support the idea of either vegetable or animal origin. These bodies do not stain with the ordinary aniline stains, but preserve their original yellow-brown colour. They are seen well in unstained sections. They give a characteristic prussian-blue reaction with potassium ferrocyanide and dilute hydrochloric acid. The reaction is not so obvious unless the solutions are slightly warmed. Where the bodies are too large to be phagocytosed by individual cells they tend to become surrounded by plasmodial masses. Many of the phagocytes contain much carbon pigment in addition. Though these bodies are mainly found in the alveoli and

infundibular passages, they are also present in the caseous areas, in the neighbourhood of the phthisical cavities, and some can be demonstrated in the fibrotic areas surrounded by definite fibroblasts. One in particular (see Fig. 12) measured about 75 μ. It is clear and segmented in its middle part, but the extremities are nodular and clubbed. It is difficult to imagine that a foreign body of such length could be transported by phagocytes, but they may represent larger bodies left in a bronchus which has become obliterated. The bodies have been examined with the micro-spectroscope, but so far no clue as to their nature has been obtained by this means. They are not refractile by polarized light.

Nature of the Bodies.

We have shown these preparations to several pathologists, but the appearances are new to them. To confirm our own opinion we have submitted them to experts in zoology, who are unanimous that they are not of animal nature. We have also submitted them to botanical and chemical authorities, and though there has been a considerable difference of opinion, some regarding them as hyphomycetes, the general opinion has been that they are not vegetable forms.

The fact that exactly similar bodies have been found in the lungs of another asbestos worker, and, so far as I can ascertain, have not been found elsewhere, would seem to indicate that they are essentially derived from or associated in some way with the asbestos itself. It is also certain that they do not in any way resemble concretions, largely composed of calcium and other salts, and also containing iron derived from blood, such as have been described as streptothrix forms in the spleen, and which may closely simulate mycelial filaments. The hypothesis advanced is that these bodies are portions of asbestos fibres in the process of alteration and absorption by hydrolysis, either by direct chemical action or by enzymes. The particular variety of asbestos with which this patient worked was a Canadian serpentine (chrysotile). It would probably contain silica and a magnesium salt in about equal proportions (40 per cent.) with up to 3 per cent. ferrous oxide, 1 per cent. of alumina, and water. From its high resistance to heat we are apt to regard asbestos as indestructible, but, given time, it is possible for hydrolysis of such silicates to occur, even in pure water. Such hydrolysis would be hastened and intensified by the presence of CO_2 in the pulmonary alveoli, and the warm moist atmosphere there would, no doubt, accelerate the process. Even under these conditions the process would necessarily be a slow one. The magnesium could be separated out as relatively insoluble carbonate, or more soluble bicarbonate, which in turn would be converted into any other salt for which there happened to be the appropriate acid available.

The iron existing in a ferrous condition in the presence of an oxidizing agent might be converted into the ferric state, and subsequently precipitated as hydroxide. The silica might pass into a colloidal state, at first in sol form (orthosilicic acid), later passing into a gel (metasilicic acid). If this were so in sol form, it would tend to remain associated with the surface of the asbestos fibre by adsorption, and might be held there till it became a gel. In time the gel might adsorb the solution, and so gradual conversion of the fibre into a mass of gel would occur. There might be in the tissues sufficient albuminoid material to effect rapid gelatinization of the sol, particularly if, as would be the case here, the sol was being slowly produced. The fact that the gel is of high surface tension, and formed at an irregular rate, would give it a spheroidal structure and account for some of the appearances seen here. Whether this be the exact explanation or no, it is at least an hypothesis which should be capable of experimental verification. As has been held by Gye and others, in cases of silicosis there may be a direct chemical action of silica on the tissues apart from the merely mechanical irritation of the particles, with the production of fibrosis. Orthosilicic acid is, as has been shown, an active poison, but rapid conversion into metasilicic acid would minimize its action.

As to the relative part played by the asbestos and the tuberculous infection in this case, in relation to the fibrous change, it is difficult to say, but it is a reasonable assumption that the tuberculosis was a superadded infection, as in Dr. Grieve's case referred to above there was in the sections examined a considerable degree of fibrosis without apparent tuberculosis. The immediate cause of death in that case was a terminal broncho-pneumonia. Till some experimental work is completed the exact nature of the foreign bodies must remain in doubt, but their highly characteristic appearance may well prove to be an important diagnostic point in the recognition of the lung of the worker in asbestos.

I am much indebted to Dr. Cooke for material from his case to Dr. Grieve for an opportunity of examining his microscopic sections, to P. L. Robinson, D.Sc., of the Chemical Department, Armstrong College, for his advice and suggestions on the chemistry of the silicates, and to Professor W. H. Lang, F.R.S., of Manchester, for a reasoned opinion as to the non-botanical nature of the foreign bodies.

CLINICAL ASPECTS OF PULMONARY ASBESTOSIS.

BY

SIR THOMAS OLIVER, M.D., F.R.C.P.,

Consulting Physician, Royal Victoria Infirmary, Newcastle-on-Tyne; Emeritus Professor of the Principles and Practice of Medicine, University of Durham.

DR. W. E. COOKE has given a short account of the history of asbestos, also of the processes of its manufacture into cloth-like structures much in the same manner as raw cotton fibre is woven. He has told us that in the carding department a considerable quantity of dust is evolved. The crushing of the rock is not carried on to any extent in this country; this is usually done in the countries where the mineral is quarried. Canadian rock is crushed in Canada so as to reduce the expense of transport to Great Britain. Our workers are therefore less exposed to the harmful influence of the dust—a fortunate circumstance, since the rock frequently contains as much as from 50 to 60 per cent. or more of silica.

With the exception of Dr. Cooke's paper on pulmonary asbestosis published in 1924, and the details of a fatal case published by Dr. Montague Murray in the *Charing Cross Hospital Gazette* in 1900, there has not been, to my knowledge, anything written in this country upon the subject. I have had, however, the opportunity of visiting asbestos factories in America, and of seeing cases of pulmonary asbestosis through the kindness of Drs. Haddow and Grieve of Armley, Leeds. It may, I think, be safely said that there must have been several deaths of workers in British factories from the malady, but as no autopsy and microscopical examinations of the lungs were made the deaths were probably certified as pulmonary tuberculosis.

Asbestos manufacture is largely a familial occupation. It has been carried on in this country only for a little over thirty years. Carding and spinning of the fibre are important processes in the manufacture of asbestos goods. In these departments many women are employed, mothers being succeeded by their daughters. Where ventilation in the carding and spinning rooms is properly attended to the atmosphere is fairly clear of dust and floating fibre, otherwise in these operations considerable quantities of dust become suspended in the atmosphere. In a British factory the dustiest process is "hand beating" of the finished mattresses used for covering and protecting the internal machinery of automobiles. This work should not be undertaken in a room separated from the main part of the factory, with open windows at one end and strong down-draughts at the other, but even with this precaution men working therein should wear masks.

Recently, with Dr. Grieve of Armley, I examined two women who are the subjects of pulmonary asbestosis, one aged 48 and the other 39. The older patient was one of the first to commence work thirty years ago in the particular factory I visited. At that date no danger from dust was anticipated, so that no effective ventilation of the workrooms was attempted, such as prevails to-day. Although only 48 the first patient mentioned looks old for by several years, and is extremely emaciated. She gave up work a year ago on account of increasing physical

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debility, shortness of breath, and cough. At present she has no expectoration; her respiratory capacity is one inch. Although the apices of both lungs in front are resonant, there is distinct flattening of the percussion note at the bases. The respiratory murmur at the apices and mid-lung is coarser than usual, and the expiratory murmur is prolonged. At the right base the respiratory murmur is feeble, and small dry friction sound is heard. Towards the base of the left lung and extending into the axilla are heard small moist tinkling sounds, suggestive of cavitation having taken place; here also small friction sounds can be heard. Similar physical signs prevail posteriorly. The apex beat of the heart is displaced upwards and outwards; it is felt external to the nipple, a circumstance which, combined with marked accentuation of the second sound of the heart heard over the pulmonary artery, suggests that fibrotic changes have already occurred in this lung. Although the patient states that she has no expectoration, this was present six weeks ago, and when examined was found to be free of tubercle bacilli. There is no enlargement of the external glands.

The other patient, aged 39, has been an asbestos worker for eighteen years. She had no illness until four years ago, when she developed cough and attacks resembling bronchial asthma. After remaining away from the factory for three months she returned to her employment, and followed the occupation for three years, when she married, and as in the early months of her pregnancy she lost considerably in weight she retired from the factory. Although reduced considerably in weight, and the subject of cough all through her pregnancy, her infant daughter, who is 14 months old, is healthy and well developed.

The patient complains of a dragging in the chest without actual pain. There is noticeable shortness of breath on slight exertion, and she complains of morning cough with expectoration. The sputum has been examined and is negative as regards tubercle bacilli. Her appetite is poor. She weighs 8 st., a drop of 3 st. having occurred within the last two years. Her heart is healthy; the apex beat is not displaced, but the second sound over the pulmonary artery is distinctly accentuated. The apices of her lungs are resonant. Here the respiratory murmur is coarser than usual and the expiratory is prolonged, so that the inspiratory and expiratory murmurs approach each other in quality. Moist râles are heard in mid-axillæ and small friction with crepitation is heard at the bases. This woman's mother, who is aged 60, is still working in the factory.

From what I have seen clinically of pulmonary asbestosis it resembles silicosis of the lungs in the marked shortness of breath on slight exertion, deficient respiratory capacity, physical debility, and, in examination of the sputa of not too far advanced cases, absence of tubercle bacilli, but since fibrotic changes are developing in both of the patients to whom I have alluded, there is almost sure to develop, if such has not already taken place, pulmonary tuberculosis.

The clinical picture of pulmonary asbestosis differs slightly from that presented by a patient the subject of ordinary tuberculosis of the lungs, in so far as there is a pronounced deadening of the skin varying from mild bronzing to slight blueness, a degree of shortness of breath in excess of the physical signs, a greater amount of general disability, little expectoration, and comparative absence of night sweats.

AN ACTIVE CONSTITUENT OF THE PREPARATION CALLED "GLUKHORMENT."

BY

H. H. DALE, C.B.E., M.D., F.R.C.P., SEC. R.S.,

AND

H. W. DUDLEY, O.B.E., M.Sc., PH.D.

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IN May of this year Professor von Noorden published in the *Klinische Wochenschrift* an account of a new pancreatic preparation which had a controlling effect on carbohydrate metabolism, but, unlike insulin, was effective when administered by the mouth.[1] To this preparation the name "glukhorment" had been given, and the title of the paper made it clear that the substance was regarded by the author as containing a new anti-glycosuric principle, naturally preformed in the body. On information, evidently supplied to him by the chemist responsible for devising "glukhorment," Professor von Noorden stated explicitly that, in spite of indications in the patent specification, which might suggest some connexion of the active principle with a guanidine derivative, no such derivative, and in particular no synthalin,* had been added; and, further, that the finished preparation contained no guanidine derivative of any kind in recognizable amount. Professor von Noorden drew the cautious conclusion that, if the activity were due to a guanidine derivative, it would have to be one of extremely high activity. In July of this year one of us (H. H. D.) received a communication from the Horment Company, who were manufacturing glukhorment, stating that they were sending material in the hope that clinical trials of it could be arranged. In due course this and several subsequent consignments of glukhorment were sent by the Horment Company, with a request for their trial.

A consideration of preliminary reports, on the mode of action of this preparation on the human being and on laboratory animals, suggested a strong similarity between its effects and those with which we had become familiar, through experiments then for some time in progress, on the action of synthalin. Some of the glukhorment was immediately placed in the hands of one physician, who will presumably report his experience with it in due course. The physiological resemblance to synthalin was so pronounced, however, that, before the question of wider clinical trials was considered, it was thought desirable to make a simple chemical examination, in order to confirm the fact that the preparation was free from synthalin and similar guanidine derivatives, as stated in the paper by Professor von Noorden, of which copies had been submitted by the Horment Company in support of their request. The result of this first test showed clearly that a guanidine derivative strongly resembling synthalin was present in substantial amount in the glukhorment tablets as submitted for trial. The evidence thus early obtained was at once so clear and so surprising that it was considered desirable to use a further quantity of the material submitted, in order to obtain precise information as to the nature of the substance in question. The isolation of the substance was made easy by the fact that the nitrate of synthalin is a remarkably insoluble salt.

Chemical Isolation from Glukhorment of a Guanidine Derivative closely resembling Synthalin.

Two hundred glukhorment tablets were powdered; the powder, weighing 60 grams, was thrown into 1 litre of boiling water and the mixture was kept gently boiling for fifteen minutes. The liquid was then filtered, while still hot, from a large mass of insoluble protein.

The filtrate was evaporated *in vacuo*, with the addition of octyl alcohol to prevent frothing, to a volume of 120 c.cm. On standing, it set to a jelly; this was warmed to 40°, when it became fluid, and concentrated nitric acid was added until the reaction of the liquid was strongly acid to Congo red. A white crystalline nitrate separated from the solution on standing, and the liquid no longer set to a jelly when cold. The crystalline material was collected by centrifuging, washed in the centrifuge with a small quantity of dilute nitric acid, and dissolved in about 25 c.cm. of hot water. This solution was boiled with charcoal and filtered. To the hot filtrate 0.5 c.cm. of 6 per cent. nitric acid was added, and the nitrate crystallized on cooling. This was filtered off and dried; it weighed 1.135 grams. It was then converted into the picrate by dissolving it in water and adding a saturated solution of sodium picrate until no further precipitate was produced. The picrate was filtered

* "Synthalin" is the synthetic compound, decamethylenediguanidine, introduced by Frank, Nothmann, and Wagner, as an antidiabetic remedy for oral administration, and already the subject of numerous reports.

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